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09/376,911	08/18/1999	FRANCIS MICHON	1758-4043US1	7105

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/376,911	Michon et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 1, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above, claim(s) *6, 7, 29-36, and 41-58* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 8-28, and 37-40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3, 4 & 7*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 08/18/99 (paper no. 1.5).

Election

2) Acknowledgment is made of Applicants' election, with traverse, of invention 18, claims 5 and 15, filed 10/01/01 (paper no. 10) in response to the restriction requirement mailed 03/28/01 (paper no. 8).

The Applicants' traversal is on the grounds that the nine saccharide species described in claim 4 is a reasonable number of species and that restriction to one of the nine saccharide species is improper. Applicants assert that a reasonable number of species may be claimed in one application, provided the application also includes an allowable claim generic to all the claimed species and all the claims to species are written in dependent form. Applicants also contend that the restriction to a single species is improper, because the nine saccharide species are described in a Markush claim, which necessarily recites the same limitations for every species. Applicants further state that restriction of claims directed to methods of making the conjugate and those directed to methods of using the conjugate is improper. Applicants point out that claims 19 and 20 are not included in the restriction requirement mailed 03/28/01 (paper no. 8).

Applicants' arguments have been carefully considered, but are non-persuasive. It is important to note that what was delineated in the action mailed 03/28/01 (paper no. 8) was **not** a species election requirement, instead, a restriction requirement. A restriction requirement is made between the inventions and not between the claims. The claims can be drafted to include multiple patentably distinct inventions, as is the case in the instant invention. Although claim 4 is drafted in a Markush format, the various saccharides recited in the claim are structurally, immunogenically and biologically distinct from one another. A structure search performed for one saccharide would not be co-extensive for the other. It is noted that in this regard that Applicants do not argue that the saccharides recited in claim 4 are not distinct from one another.

With regard to the issue of linking claims, no linkage exists if the linking concept is non-

patentable, i.e., already known in the art. As is clear from the various art rejections documented below, the linking concept in the instant application is known in the art, and therefore the linking claims are currently non-allowable. However, upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicants are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Although Applicants state that separating the claims drawn to a claimed product from claims directed to methods of using the product and to a method of making the product is improper, Applicants do not advance any arguments in support of their statement. As clearly set forth in the restriction requirement mailed 03/28/01, the product(s) of the invention and the process of using or making the product(s) were properly restricted into separate invention groups as is permitted under M.P.E.P. 806.05(h) and M.P.E.P. 806.05(f).

With regard to claims 19 and 20, these claims were inadvertently left out of the restriction requirement mailed 03/28/01. These claims are now included in the list of linking claims that includes claim 16.

For the reasons explained above, the restriction requirement of record is maintained and is hereby made FINAL.

Status of Claims

3) Claims 1-58 are pending.

Claims 6, 7, 29-36 and 41-58 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 5 and 15, encompassing group B streptococcus type III polysaccharide

conjugate, and the linking claims 1-4, 8-14, 16-28 and 37-40 are under examination. An action on the Merits for these claims is issued.

Drawings

4) The drawing is not objected to by the Draftsperson under 37 C.F.R 1.84 or 1.152 and as such, the drawing has been approved as formal drawing.

Information Disclosure Statements

5) Acknowledgment is made of Applicants' information disclosure statements filed 05/24/00, 12/07/99 and 03/01/01 (paper no. 3, 4 and 7). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 11).

Priority

6) This application claims domestic priority to the non-provisional application, SN 60/097,120 filed 08/19/1998.

Specification - Informalities

7) The instant specification is objected to for the following reason(s):

(a) The amendment to the first paragraph of the specification introduced via the paper filed 08/18/99 (paper no. 1.5), wherein the instant non-provisional application is stated to be a continuation-in-part of an abandoned provisional application, is objected to. An application claiming the benefits of a provisional application under 35 U.S.C. 119(e) should not be called a "continuation" of the provisional application since an application that claims benefit of a provisional application is a non-provisional application of the provisional application, not a continuation, division, or continuation-in-part of the provisional application. The first paragraph of the specification should be amended to state that the instant application claims priority to the provisional application SN 60/097,120, filed 08/19/1998.

(b) The use of trademarks in the instant specification has been noted in this application. For example, see page 22, line 13: "Tween 20"; page 21, line 9; page 20, line 14; and page 18, line 22: "Superdex 200"; page 18, line 17: "superose 12"; page 21, line 1: "Centricon 30"; and page 20, lines 24 and 30: "zwittergent 3-14". The recitations should be capitalized wherever they appear and be accompanied by the generic terminology. Each letter of

the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix l. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever such recitations appear.

(c) The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). The recitation in the instant claims of "N-propionated polysaccharide" or "N-propionated oligosaccharide" does not appear to have antecedence in the specification. For the record to be clear and complete, the page and line number where the specification teaches this limitation should be indicated.

(d) The instant specification uses certain abbreviated terminologies that are not understood. For example, "DCC" in line 1 on page 9 and lines 5 and 23 of page 57. Clarification/correction is requested.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

8) Claims 18 and 20 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a polysaccharide-protein conjugate or oligosaccharide-protein conjugate wherein the conjugation is conducted at a pH of above 9.0 in a non-phosphate buffer, such as, borate or carbonate budder, does not reasonably provide enablement for such a conjugate wherein the conjugation is conducted at a pH of 7.0 and in a phosphate buffer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;

The nature of the invention;
The state of the art;
The relative skill of those in the art; and

- The breadth of the claims.

In the instant case, the recitation in claims 18 and 20, and the descriptive statement on page 10, lines 17-19 and 25-27 that the method of conjugation is conducted at a neutral pH of about 7.0 and in a phosphate buffered reagent, are not commensurate in scope with the evidence. Instant Examples describe N-acryloylated polysaccharide- or oligosaccharide-protein conjugates wherein the conjugation was conducted by Michael addition at a pH of 9.5, or between about 9.0 and about 10.0 (see page 10) in a borate or carbonate/bicarbonate buffer. However, there is no showing that an N-acryloylated polysaccharide or oligosaccharide is conjugated to a protein by Michael addition at a pH of "about 7.0" and in a phosphate buffer medium. This is important because there is no certainty that this type of conjugation could optimally and/or effectively be conducted at a non-alkaline pH. The art indicates that conjugation by Michael addition is carried out in the alkaline range, i.e., above 9.0 in an appropriate buffer, such as, borate or carbonate buffer. For instance, Romanowska *et al.* (*Methods in Enzymol.* 242: 90-101, 1994 - Applicants' IDS) used a pH of 8.5, 9.5 and 10.5 for this type of conjugation (see page 94) and found a pH of 10.0 or 10.5 to be optimal for coupling, which pH prevented protein degradation (see page 101). Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 1709-1711, 1990) teach that N-acryloylated oligosaccharide can be covalently conjugated to a protein by Michael reaction at a pH greater than 8.0 to 8.5 and at 10.5 (see page 1710). Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) teach that even at a pH of 8.0 or 9.0 in phosphate buffer, the Michael reaction did not furnish appreciable conjugation; the reaction however proceeded smoothly at these two pH in carbonate buffer. Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) also teach that a very small amount of carbohydrate was conjugated in borate buffer at pH 8.0 (see paragraph bridging pages 537 and 538). Pon (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) teaches that phosphate buffers at various pH values did not prove satisfactory during the conjugation process (see page 147, lines 2-4).

Undue experimentation would have been required to practice the invention as claimed due to the lack of guidance/evidence, lack of working examples, the uncertainty with regard to

conjugation by Michael addition taking place at a non-alkaline pH of 7.0 and in a phosphate buffer medium and the quantity of experimentation necessary.

9) Claims 25 and 40 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition or a vaccine comprising a non-combination, i.e., a single conjugate component vaccine, comprising an N-acryloylated polysaccharide or oligosaccharide conjugated to a protein as claimed, does not reasonably provide enablement for such a composition or vaccine further comprising a second, conjugated or unconjugated vaccine component, for example, DTPa-Hib or DTaP-IPV-Hib, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art; and
- The breadth of the claims.

In the instant case, there is a lack of showing that an N-propionated polysaccharide- or oligosaccharide-protein conjugate of the instant invention can successively be combined with a second component, such as, DTP, DTaP, Td, DTap-Hib, DTaP-IPV-Hib and combinations thereof. There is no showing that the instantly claimed conjugate when combined with one or more of any of the recited second component would retain its function as a vaccine and would effectively elicit an optimal immune response, particularly a polysaccharide- or oligosaccharide-specific protective immune response. This is important because the art of combination vaccines indicates the occurrence of potential interference by one or more added vaccine components. For instance, Barrington *et al.* (*Infect. Immun.* 61: 432-438, 1993) teach that immunizations of conjugated polysaccharides and unconjugated (free) carrier protein (for example, TT in the

instant case), lead to a non-epitope specific suppression of the antibody response not only to the carrier protein, but the polysaccharide as well. Corbel (*Biologicals* 22: 353-360, 1994) teaches that the use of diphtheria and tetanus proteins as carriers for multiple polysaccharide conjugates may lead to epitope suppression of anti-polysaccharide responses (see abstract). In the instant case, for example, there is no showing that the instantly claimed conjugate when combined with a preparation containing Hib conjugate, i.e., DTap-Hib or DTaP-IPV-Hib, would not result in a similar polysaccharide-suppressing effect. Corbel further teaches that the formulation of the combinations may present specific problems resulting from the interaction of the various components with each other and with the adjuvants and excipients (see page 353). Given the lack of evidence/guidance, the teachings in the art of potential interference by one or more added vaccine components and suppression of antibody response to the polysaccharide or the carrier protein, the breadth of the claims, the lack of working examples and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to practice the invention as claimed.

10) Claims 37-40 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a conjugate vaccine comprising, for example, an N-acryloylated group B streptococcus type III polysaccharide conjugated at the beta position to tetanus toxoid, said vaccine capable of inducing a homologous polysaccharide-specific opsonophagocytic antibody response, does not reasonably provide enablement for such a vaccine comprising any N-acryloylated bacterial polysaccharide or oligosaccharide similarly conjugated to a protein carrier and is further capable of providing "protective immunity against" any "disease causing organism or cell", as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

> The quantity of experimentation necessary (time and expense);
> The amount of direction or guidance presented;
> The presence or absence of working examples of the invention;
> The nature of the invention;

- The state of the art;
- The relative skill of those in the art; and
- The breadth of the claims.

In the instant case, claims 1 and 16 broadly encompass a vaccine that "provides protective immunity against a disease causing organism", such as, "bacteria" including "Streptococcus". A myriad of "disease causing organisms" and "bacteria" and any number of serogroups, types or species of "Streptococcus" are encompassed in the scope of the claims against which the claimed polysaccharide- or oligosaccharide-protein conjugate vaccine is required to confer "protective immunity". The limitation "disease causing organism" encompasses viruses, fungi, parasites etc., The limitation "disease causing bacteria" encompasses Gram positive bacteria, Gram negative bacteria, anaerobic bacteria etc., Both homologous and heterologous "disease causing organism", "bacteria" or "Streptococcus" are encompassed in the breadth of the claims. The limitation "Streptococcus" encompasses multiple species, such as, *Streptococcus pyogenes*, *Streptococcus mutans*, *Streptococcus faecalis* etc., The terms "polysaccharide" and "oligosaccharide" encompass lipopolysaccharide, capsular polysaccharide, a cell wall polysaccharide, exopolysaccharide etc. The protective ability of any polysaccharide of a disease-causing organism, bacteria or *Streptococcus* is not a predictable. The data provided for a *Streptoccus* in Table 6 shows that the N-acryloylated group B *Streptococcus* type III capsular polysaccharide conjugated to tetanus toxoid by Michael addition, on administration along with alum to laboratory animals, elicited homologous GBS type III capsular polysaccharide-specific opsonophagocytic antibody response as measured on day 52 post immunization. However, there is no evidence that this conjugate would induce anti-capsular polysaccharide opsonophagocytic antibodies that would protect against any "disease causing organism", "disease causing bacteria" or any "Streptococcus" other than a disease-causing group B streptococcus type III. This is important because, by and large, the opsonophagocytic anti-capsular polysaccharide antibodies induced by a conjugate vaccine comprising the corresponding polysaccharide or oligosaccharide are bacteria-, group- or serotype- or species-specific. For instance, an *E. coli* O111 O-specific oligosaccharide conjugate would not be expected to provide protective immunity against another strain of the same bacterium, *E. coli* serotype O157, for example. From what is known in the art

about the polysaccharide-specific opsonophagocytic response against a particular bacterial pathogen, it is unlikely, for example, that a GBS III capsular polysaccharide-TT conjugate would induce antibodies that are opsonophagocytic against heterologous streptococci, for example, GBS II, GBS V or GBS VIII streptococci, or Group C streptococci, or against a heterologous disease-causing bacterial pathogen, such as, *Staphylococcus* or *Salmonella*. Neither there is evidence, nor is it predictable that a non-capsular polysaccharide, for example, of GBS III when conjugated as described in the instant case, would provide "protective immunity against" homologous or heterologous disease-causing bacteria. Therefore, undue experimentation would have been required by one skilled in the art at the time the invention was made to practice the full scope of the invention due to the lack of evidence/guidance within the instant specification, the lack of working examples enabling the full scope of the claimed invention, the unpredictatbility factor, the breadth of the claims and the quantity of experimentation necessary.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

11) Claims 1-5, 8-28 and 38-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1 and 16 are vague in the recitation "directly conjugated to", or "directly conjugated", because it is unclear what does direct conjugation encompass. Does it mean that no spacer or any such molecule is used to couple the polysaccharide or oligosaccharide to the protein, or does it mean that the polysaccharide or oligosaccharide is conjugated to a protein without further activation, oxidation or any treatment with agents, such as, EDAC, sodium cyanoborohydride etc.? Clarification is requested.

(b) Claims 2-5, 8 and 11-13 lack proper antecedence for the recitation "A polysaccharide-protein conjugate according to claim .....". To be consistent with the claim language used in claims 9, 10, 14, 17, 18 and 21, and for proper antecedence, it is suggested that Applicants replace the recitation "A polysaccharide-protein conjugate according to claim ....." with --The polysaccharide-protein conjugate according to claim .....--.

(c) Claims 38-40 lack proper antecedence for the recitation "A vaccine according to

claim .....". For proper antecedence and similar to the claim language used in claims 27 and 28, it is suggested that Applicants replace the recitation "A vaccine according to claim ....." with --The vaccine according to claim .....--.

(d) Claims 3-5 and 17 are vague and indefinite in the recitation "derived", because it is unclear what the process of "deriving" encompasses: extraction, separation, purification or modification?

(e) Claim 20 is vague and confusing in the recitation "carbonate/bicarbonate buffer" (see line 3), because it is unclear what this limitation encompasses. It is not clear whether "/" represents "or" or "and". Does this limitation mean carbonate buffer or bicarbonate buffer, carbonate buffer and bicarbonate buffer, or a buffer containing both carbonate and bicarbonate components?

(f) Claim 24 contains incorrect Markush claim language: "selected from the group consisting of alum **or** stearyl tyrosine" [Emphasis added]. When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, "wherein R is a material selected from the group consisting of A, B, C **and** D" is a proper limitation; "wherein R is a material selected from the group consisting of A, B, C or D" is an improper limitation.

(g) Claims 25 and 40 are vague and confusing in the use of abbreviated recitations in the claim language (see line 3), because it is unclear what these abbreviations mean. It is suggested that Applicants use the full terminology at first occurrence in the claim(s), with the abbreviation retained in parenthesis.

(h) Claims 5 and 15 are confusing in the inconsistent recitation of "type III" (see claim 15) and "serotype III" (see claim 5) while referring to Group B streptococcus.

(i) Claims 9, 10, 14 and 18-28 are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form

the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13) Claims 1-4, 8, 11-14, 22 and 26-28 are rejected under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 264-265, 1993) (Roy *et al.*, 1993).

Roy *et al.* (1993) teach a group B meningococcal polysaccharide conjugate vaccine comprising an N-acryloylated mono- and poly-alpha-(2,8)-sialic acid or colominic acid antigen directly conjugated to a protein, such as, BSA, poly-L-lysine or tetanus toxoid by Michael addition via thiol or amine groups. The conjugation was conducted in borate buffer at pH 9.2. The conjugate is present in 5 mmol sodium chloride, i.e., saline (i.e., pharmaceutically acceptable carrier). The colominic acid-tetanus toxoid conjugate induced IgG and IgM monoclonal antibodies in mice and therefore served as an immunogen (see pages 264 and 265; and Figures).

Claims 1-4, 8, 11-14, 22 and 26-28 are anticipated by Roy *et al.* (1993).

14) Claims 1-3, 14 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 536-538, 1991) (Roy *et al.*, 1991).

Roy *et al.* (1991) teach antigenic carbohydrate protein conjugates comprising synthesized *N*-acryloylated sugars directly conjugated at the beta position to a lysine-containing protein, such as BSA, through the epsilon amino group. The conjugates are HPLC-purified using NaCl and phosphate buffer (i.e., a pharmaceutically acceptable carrier). The antigenicities of the conjugates were demonstrated by double radial immunodiffusion. Polymer conjugates were also prepared. See pages 536-538; and Figures on page 537.

Claims 1-3, 14 and 22 are anticipated by Roy *et al.* (1991).

15) Claims 1-4, 8, 11-14, 16, 17 and 19-22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992).

Pon teaches polysaccharide or oligosaccharide-protein conjugates (i.e., oligosialic or polysialic conjugates) produced via Michael type addition for use as a vaccine effective against *Escherichia coli* K1 and serogroup B *Neisseria meningitidis* (see page 14; Chapter 2; section

4.2.3.3 and Tables 4-5). The conjugates comprise an N-acrylyolated K1 polysaccharide or oligosaccharide, isolated or synthesized, directly conjugated to a protein, such as, bovine serum albumin (BSA), a porcine IgG or tetanus toxoid (TT) by Michael-type addition via the epsilon free amino of a lysine residue. The conjugation was performed at a pH of above 9, i.e., 9.2, in borate buffer. See sections 4.2.3.3 and 2.2.1.3; and page 56. The conjugate was produced by a method comprising de-N-acetylating the polysaccharide or oligosaccharide using a de-N-acetylating base reagent, such as, NaOH, followed by N-acryloylating the de-N-acetylated polysaccharide or oligosaccharide with an acryloylating reagent, such as, acryloyl chloride and directly conjugating the resultant polysaccharide or oligosaccharide (i.e., N-propionated) to a protein (see page 39; Table 2-3; sections 2.2.2.1 and 2.2.2.5; and section 4.2.3.3).

That *E. coli* K1 is a bacterium, that colominic acid or *E. coli* K1 polysaccharide is a glycosaminoglycan and that the polysaccharide or oligosaccharide is conjugated to the protein at the beta-position of the propionate moiety, are inherent from the teachings of Pon. Note that Pon teaches *E. coli* K1 capsular polysaccharide as being known as colominic acid (see page 8; and page 9 above Figure 1.2).

Claims 1-4, 8, 11-14, 16, 17 and 19-22 are anticipated by Pon.

16) Claims 1-3, 8, 11-14 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 1709-1711, 1990) (Roy *et al.*, 1990).

Roy *et al.* (1990) teach conjugates comprising *N*-acryloylated sialic acid- (N-acetylneuraminic acid) and sialylooligosaccharide-protein lactoside directly conjugated to lysine groups of proteins, such as, BSA or tetanus toxoid, by Michael addition. The reaction is conducted in borate or carbonate buffer at pH 10.0 (see abstract; page 1711 and Schemes 1-3) or at pH greater than 8.0-8.5 (see page 1710). The conjugate as eluted is present in water (i.e., a pharmaceutically acceptable carrier). The conjugates were demonstrated to be antigenic using serological lectin binding assays. Roy's teaching that work was in progress to evaluate the immunogenicities of the protein conjugates (see page 1711) indicates that the conjugates were meant for use as immunogens or vaccines.

Claims 1-3, 8, 11-14 and 22 are anticipated by Roy *et al.* (1990).

17) Claims 1-3, 8, 11-14 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Romanowska *et al.* (*Methods in Enzymol.* 242: 90-101, 1994 - Applicants' IDS).

Romanowska *et al.* teach artificial N-acryloylated sialic acid, sialoside and a T antigen derivative [beta-D-Gal-(1->3)-alpha-D-GalNAc] conjugated directly to bovine serum albumin, tetanus toxoid or poly(L-lysine) via epsilon amino groups. The conjugation utilizes the addition of the epsilon-amino or thiol group of lysyl residues on proteins on to N-acryloylamido substituted glycosides to act as efficient nucleophiles in the Michael addition (see pages 91 and 92; Schemes 1-3; and pages 97-101). The conjugation is conducted at a pH of 8.5, 9.5 or 10.5 (i.e., above 9.0) in carbonate or borate buffer. The conjugate is present in water, i.e., pharmaceutically acceptable carrier (see pages 94, 97 and 100).

Claims 1-3, 8, 11-14 and 22 are anticipated by Romanowska *et al.*

18) Claims 1-4, 11-14 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Auzanneau *et al.* (*Bioorg. Medicinal Chem.* 4: 2003-2010, 1996).

Auzanneau *et al.* teach *N*-acryloylated Group A streptococcal cell wall oligosaccharide conjugated directly to bovine serum albumin or ovalbumin via the addition of ε-amino groups of lysines present on the protein (see abstract; and Figures in 2004 and 2005). The acryloylating reagent used is acryloyl chloride (see page 2005, right column and page 2008). The conjugation was conducted in carbonate buffer at pH 10.0 (see paragraph bridging pages 2005 and 2006; and page 2009). The glycoconjugate is contained in distilled water (see page 2009, left column). The use of soluble glycoconjugates produced by this method as immunizing antigens (i.e., immunogens or vaccines) was contemplated (see page 2007, left column). Auzanneau *et al.* teach that conjugate "addition of *N*-acryloylated oligosaccharides is also a widely used strategy to couple an oligosaccharide to a protein". That the prior art oligosaccharide, as treated, yields *N*-propionated oligosaccharide and that it is conjugated at the beta-position of the propionate is inherent from the teachings of Auzanneau *et al.*

Claims 1-4, 8, 11-14 and 22 are anticipated by Auzanneau *et al.*

19) Claims 1-3, 8 and 11-14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*Bioorg. Medicinal Chem. Lett.* 2: 911-914, 1992) (Roy *et al.*, 1992).

Roy *et al.* (1992) teach neoglycoproteins (i.e., conjugates) comprising N-acryloylated carbohydrate T antigen (beta-D-Gal-(1->3)-alpha-D-GalNAc), or a blood group trisaccharide determinant (beta-D-Gal-(1->4)-beta-D-GlcNAc-(1->6)-alpha-D-GalNAc) conjugated by Michael addition to a protein carrier, such as, tetanus toxoid via epsilon-lysine-NH2 or cysteine-SH groups. The conjugation was conducted in carbonate buffer at pH 10.0 (see abstract; and pages 912-914). Roy's teaching that the immunogenicities of the protein conjugates were being evaluated (see page 913) indicates that the conjugates were meant for use as immunogens or vaccines.

Claims 1-3, 8 and 11-14 are anticipated by Roy *et al.* (1992).

Rejection(s) under 35 U.S.C. § 103

20) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

21) Claims 1 and 8-10 are rejected under 35 U.S.C § 103(a) as being unpatentable over Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) in view of Blake *et al.* (US 5,439,808).

The teachings of Pon are explained above which do not disclose the conjugates wherein the protein is a recombinant *N. meningitidis* outer membrane protein.

However, the use of a recombinant *N. meningitidis* outer membrane protein for the production of a polysaccharide-protein conjugate is conventional and is well known in the art of

conjugate vaccines. For instance, Blake *et al.* teach a recombinant outer membrane protein of *N. meningitidis* and its use in the production of a polysaccharide-protein conjugate, including that of a bacterial polysaccharide conjugate, such as a group B meningococcal capsular polysaccharide. See the fourth full paragraph in column 9.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace Pon's protein carrier with Blake's recombinant *N. meningitidis* outer membrane protein to produce the product of the instant invention with a reasonable expectation of success. Substitution of one protein carrier with another, alternative, art-known protein carrier that accomplishes the same or similar carrier effect would have been obvious to a skilled artisan and would have expected to yield a similarly effective product.

Claims 1 and 8-10 are *prima facie* obvious over the prior art of record.

22) Claims 1, 16 and 22-24 are rejected under 35 U.S.C § 103(a) as being unpatentable over Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) and Blake *et al.* (US 5,439,808).

The teachings of Pon are explained above which do not teach the conjugate composition further comprising an adjuvant, such as, alum or stearyl tyrosine.

However, it is conventional to use microbial polysaccharide-conjugates along with an art-known, routinely used adjuvant, such as, alum or stearyl tyrosine, wherein the adjuvant is added to enhance antibody production. For instance, Blake *et al.* teach the use of alum or stearyl tyrosine along with a composition comprising a microbial polysaccharide-conjugate. See the last two paragraphs in column 10 of Blake *et al.*

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add Blake's adjuvant, such as, alum or stearyl tyrosine, to Pon's conjugate composition to produce the composition of the instant invention with a reasonable expectation of success. Since the addition of a conventional adjuvant to a conjugate composition is routinely practiced in the art, one skilled in the art would have been motivated to produce the instant invention for the expected benefit of enhancing antibody production to the composition as taught by Blake *et al.*

Claims 1, 16 and 22-24 are *prima facie* obvious over the prior art of record.

Objection(s)

23) Claims 5, 8, 15, 22, 26, 37 and 38 are objected to for the following reasons:

(a) In claims 37 and 38, for clarity, it is suggested that Applicants replace the recitation "disease causing organism" with --disease-causing organism--.

(b) Claims 5 and 8 are objected to for the inconsistent recitation: "Group B streptococcus" in claim 5 and "group B *Streptococcus*".

(c) Claim 15 is objected to for the inconsistent recitations: "Group B streptococcus" in line 3 and "Group B Streptococcus" in line 4 of the claim.

(d) Claim 26 is objected to for the incorrect recitation "A immunogen" (see line 1). To obviate the objection, it is suggested that Applicants replace the recitation with --An immunogen--.

(e) Claims 22 and 26 are inconsistent with claim 37 with regard to the recitation "claims 1 or 16" [Emphasis added].

(f) Claim 5 is objected to for being dependent from a rejected claim.

(g) Claim 15 is objected to for including one or more non-elected inventions. Claim 15 is further objected to for lacking antecedent basis in the specification for the limitation: "N-propionated". Note that 37 CFR 1.75(d)(1) provides, in part, that "the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description".

Relevant Prior Art

24) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Jennings *et al.* (WO 96/40239 - Applicants' IDS) disclose an *N*-acyl modified group B meningococcal polysaccharide, for example, *N*-acryloylated group B meningococcal polysaccharide (GBMP) conjugated to a protein carrier, such as, tetanus toxoid, diphtheria toxoid, CRM197 and meningococcal outer membrane protein. The GBMP was first *N*-deacetylated and then treated with acryloyl chloride at a pH of 8.5 and then conjugated to tetanus toxoid. The conjugate is purified and equilibrated in PBS (i.e., a pharmaceutically acceptable carrier). The conjugate was used to immunize mice with or without adjuvants, such as, alum or

stearyl tyrosine, wherein the conjugate induced group B meningococcal bactericidal antibodies (see Examples 1-4 and 7; page 8, lines 19-23; Tables 1-3; and page 10). The *N*-acryloyl GBMP-tetanus toxoid conjugate, its use in immunizing mice with or without alum and its ability to induce anti-group B meningococcal bactericidal and protective antibodies, that are significantly less cross-reactive with the native GBMP, are described in Example 7 and Tables 1-3.

- Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 536-538, 1991) teach that the use of N-acryloylated precursors has distinct advantages over previous methodologies since, as originally proposed, these conjugated precursors offer two synthetic possibilities. It is taught that they can be efficiently polymerized with acryloyl-type monomers and secondly, amine groups of proteins or of functionalized polymers can be used as nucleophiles to give glycoconjugates by Michael addition (see page 537, right column).

- Roy *et al.* (*Glycoconjugate J.* 7: 3-12, 1990 - Applicants' IDS) teach the production or synthesis of a poly-alpha(2-8)-*N*-acryloylneuraminic acid or an *N*-acryloylated sialic acid derivative (see pages 5-7; and Figure 2). It is taught that protein conjugates of the derivative have been prepared (see page 10). The colominic acid is first de-*N*-acetylated and then *N*-acylated or *N*-acryloylated using acryloyl chloride (see pages 4-7).

Remarks

25) Claims 1-5, 8-28 and 37-40 stand rejected.

26) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

27) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.45 a.m to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

[redacted]

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January 2002

S. DEVI, PH.D.
PRIMARY EXAMINER